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| 09/910,208 | 07/20/2001 | Jiro Hitomi | MM4454 | 4894 |

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| EXAMINER | |
|---|---|
| HADDAD, MAHER M | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/910,208 | HITOMI ET AL. | |
| | Examiner | Art Unit | |
| | Maher M. Haddad | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *December 04, 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *22-26* is/are pending in the application.

4a) Of the above claim(s) *24-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/13/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 04, 2008 has been entered.

2. Claims 22-26 are pending.

3. Claims 24-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 22-23 are under examination as they read on an antibody with binding affinity to a protein encoded by SEQ ID NO: 1.

5. Applicant's IDS, filed 10/13/08, is acknowledged.

6. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Figures 1-2, on page 3, lines 15-32 has describe the amino acid sequence of bovine calcium-binding protein that must have a sequence identifier. Correction is required. The amendment to the specification filed 9/22/05 fails to provide sequence identifier for the amino acid sequence of the bovine calcium-binding protein in figure 1.

7. The amendment filed 9/22/05 and 3/27/07 are objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

i) The amendment filed on 3/27/07 to the computer readable form of the "Sequence Listing" with SEQ ID NO: 19 and 20 represents a departure from the specification and the claims as originally filed. Applicant does not point out for support for the newly added sequences. It is noted that the new SEQ ID NO: 19 contains $^{17}$Glu, which was not found in original SEQ ID NO: 19 ($^{17}$Gln). Further, new SEQ ID NO: 20 contains $^{65}$Asn, which was not found in original SEQ ID NO: 20 ($^{65}$Gln). The specification and the claims as originally filed have no support for the new replacement of SEQ ID NO: 19 and 20.

ii) Further, it is noted that the amendment to the specification filed 9/22/05 to page 3, ¶5 (Fig. 2), points to SEQ ID NO:2 as the amino acid sequence of bovine calcium-

binding protein. However, SEQ ID NO: 2 is only 50 amino acids in length and do not correspond to the nucleic acids sequence in figures 1 or 2.

iii) The amendment filed on 9/22/05 to the specification on page 5, ¶3, substituting SEQ ID NO:1 or 12 for SEQ ID NO: 19 or 20 represents a departure from the specification and the claims as originally filed. The specification and the claims as originally filed have no support for the new replacement of SEQ ID NO: 1 or 12 with SEQ ID NO: 19 or 20. It is noted that there is no 1:1 correspondence between SEQ ID NO: 1 or 12 and SEQ ID NO: 19 or 20, respectively.

Applicant's arguments, filed 12/4/08, have been fully considered, but have not been found convincing.

Applicant points to Dr. Hitomi's Declaration attesting to the fact that the sequence ID provided on 12/6/06 is inaccurate, and that the original SEQ ID and SEQ ID dated 3/7/07 are identical and are the ones to be considered during the prosecution of this application.

However, Dr. Hitomi Declaration filed 12/04/08, is insufficient to overcome the objection to the specification under 35 USC 132 because besides the assertion the correct SEQ ID's for both SEQ ID 19 and SEQ ID 20 correspond directly with the sequence listing in application as originally filed and on March 7, 2007, respectively. No evidence was provided to corroborate the facts. The facts that there is no one to one correspondence between SEQ ID NO:1 and 19. Applicant does not explain the discrepancy in the Fig. 1-2 and the patented SEQ ID NO: 19 and the instantly claimed SEQ ID NO: 19 and 20.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:
*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

9. Claims 22-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed. *This is a New Matter rejection for the following reasons*:

The phrases "SEQ ID NO: 19" claimed in claims 22-23 and "these lineages" claimed in claim 22, line 3 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 3/27/07 and 12/4/06 does not point to the specification for support for the newly added limitations "SEQ ID NO: 19" claimed in claims 18 and 21 and "these lineages" as claimed in claim 22. It is noted that the new SEQ ID NO: 19 contains $^{17}$Glu, which

was not found in original SEQ ID NO: 19 ($^{17}$Gln). However, the specification does not provide a clear support of such limitation. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

Applicant's arguments, filed 12/4/08, have been fully considered, but have not been found convincing.

Applicant submits that upon review of the record it is clear that the original sequence ID provided to the Office and the subsequent sequence ID provided to the Office on 3/7/07 are identical while the sequence ID provided to applicant by the Office dated 12/6/06 is inaccurate, and is responsible for the inconsistencies pointed out by the Examiner. Applicant points to Dr. Hitomi decoration stating that the sequence ID provided on 12/6/06 is inaccurate, and that the original SEQ ID and the SEQ ID dated 3/7/07 are identical and are the only ones to be considered during the prosecution of this application.

However, Dr. Hitomi's Declaration filed 12/04/08, is insufficient to overcome the objection to the specification under 35 USC 132 because besides the assertion the correct SEQ ID's for both SEQ ID 19 and SEQ ID 20 correspond directly with the sequence listing in application as originally filed and on March 7, 2007, respectively. No evidence was provided to corroborate the facts. The facts that there is no 1:1 correspondence between SEQ ID NO:1 and 19. Applicant does not explain the discrepancy in the page 51 of the specification, Fig. 1-2 and the patented SEQ ID NO: 19 and the instantly added SEQ ID NO: 19. As stated in the previous Office Action (1) Fig. 1 and 2 depicts amino acid of 17 as Gln (Q) not Glu (E) as claimed. (2) the parent application 09/270,455, now Pat 6,313,267 and 08/568,310 12/06,310, now 5,976,832 list position 17 of SEQ ID NO: 19 as Gln (Q) not as Glu (E) as claimed. (3) SEQ ID NO: 1 encoding SEQ ID NO: 19 in the "Sequence Listing" lists the codon CAG which code for $^{17}$Gln (Q) not $^{17}$Glu (E) as claimed. (4) SEQ ID NO: 1 does not encode SEQ ID NO: 19. Applicant did not provide any evidence that the newly added SEQ ID NO: 19 is the accurate one.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

*(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

11. Claims 22-23 stand rejected under 35 U.S.C. 102(b) as being anticipated by Guignard *et al* (European Journal of Clinical Investigation, Vol:24, Supl. 2, pp.211, 1994), as is evidenced by Guignard *et al* (July 1995), Yamamura *et al* and instant specification on page 40, lines 6-10.

Guignard et al (l 994) teach a polyclonal antibody (anti-P8 or anti-MRP-8), identify an unknown protein of 6.5 kDa (P6). Guignard et al also teaches that the P6 protein identified by N-terminal amino acid sequence analysis appeared to be a new protein of the S100 family (calcium-binding

proteins). Further, Guignard et al concluded that a new protein of 6.5 kDa belonging to the S100 family was evidenced in human neutrophils (see abstract in particular). While the Guignard et al is silent as to the "bCAAF1" per se; P6 has the same N-terminal amino acid sequence encoded by hCAAF1 as is evidenced by Guignard et al (1995) that the p6b N-terminal sequence (p6b) TKLEEHLEGIVNIFHQYSVR (see Figure 3, at page 398 in particular) which is 100% identical to amino acids 2-21 of the amino acid encoded by hCAAF1. Further evidence that the amino acid sequence encoded by hCAAF1 is p6 protein came from Yamamura et al who teach that Guignard et al (1995) isolated and partially characterized a novel human calcium- binding protein that cross-reacted with an antibody against MRP8. Yamamura et al concluded that the identified N-terminal 20 amino acid sequence of the reported protein was identical to that of human CAAF1, suggesting that this protein is hCAAF1 (see page 359, lines 4-8 in particular). Given that the human and the bovine CAAF1 share 66% identity, the reference polyclonal antibody would bind to bovine CAAF1 in the absence of evidence to the contrary.

It is noted that MRP-8 (S100A8) shares only 40% sequence homology to the human S100A12 (hCAAF1). Yet, anti-MRP-8 antibodies cross-react with the human CAAF1.

SEQ ID NO: 20-S100 calcium-binding protein A8 (MRP-8) (NP_002955) (38.5%)

```
Qy          1 MTKLEEHLEGIVNIFHQYSVRKGHFDTLSKGELKQLLTKELANTIKNIKDKAVIDEIFQG 60
              :|:||: |  |::::|:|||: ||:|  : : :|||:||  |    |:    |   |  |:
Db          2 LTELEKALNSIIDVYHKYSLIKGNFHAVYRDDLKKLLETECPQYIR----KKGADVWFKE 57

Qy         61 LDANNDEQVDFQEFISLV----AIALKAAHYHTHKE 92
              || | |  |:|||||: ||       | | :|  :|||
Db         58 LDINTDGAVNFQEFLILVIKMGVAAHKKSHEESHKE 93
```

SEQ ID NO: 19-S100 calcium-binding protein A8 (MRP-8) (NP_002955) (35.9%)

```
Qy          1 MTKLEDHLEGIINIFHEYSVRVGHFDTLNKRELKQLITKELPKTLQNTKDQPTIDKIFQD 60
              :|:||  |  ||:::|:|||:  |:|  : : :|||:|:  | |: ::    :   |  |::
Db          2 LTELEKALNSIIDVYHKYSLIKGNFHAVYRDDLKKLLETECPQYIR----KKGADVWFKE 57

Qy         61 LDADKDGAVSFEEFVVLVSRVLKTAHIDIHKE 92
              || : ||||:|:||::|| ::   ||   |:|
Db         58 LDINTDGAVNFQEFLILVIKMGVAAHKKSHEE 89
```

Further evidence is provide by Applicant's specification on page 40, lines 6-9 that the existence of antigen reacting with CAAF1-22-5 monoclonal antibody in human tissue strongly suggests the existence in human tissue of a protein (human CAAF1) homologous with bovine CAAF1. Accordingly, given the high sequence identity/homology (66%) between the referenced/claimed P6 protein; the referenced antibodies would have the inherent property of binding bovine CAAF1 in the absence of objective evidence to the contrary. Moreover, given that the antibody raised against S100A8 (Guignard et al, 1995) cross-reacted with P6 (human CAAF1), the reference antibody would bind to claimed bovine CAAF1, in the absence of evidence to the contrary.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to the SEQ ID NO:19 recited in the claim. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

12. Claims 22-23 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kelly *et al* (J. Patho. 1989) as is evidenced by Guignard et al (Feb 1996).

Kelly et al teach monoclonal antibodies to study the expression of calgranulins by keratinocytes in inflammatory dermatoses. Kelly et al also teach that calgranulins are intracellular calcium binding proteins which have inflammatory cytokine activity. Further, Kelly et al teach that MAC 387 monoclonal antibody that recognizes a molecule probable containing both calgranulin A and B (see abstract in particular). MAC 387 monoclonal antibody also binds amino acid sequence encoded by SEQ ID NO: 19, as is evidenced by Guignard et al (Feb 1996) that the immunoreactivity of MAC 387 was compared with that of a polyclonal antibody raised against purified MRP-8, but cross-reacting with MRP-14, and p6 (hCAAF1/S100A12), a novel S100 protein. Under such conditions, Mac 387 was found to recognize the three S 100 proteins (see abstract in particular). Guignard et al concluded that the MAC 387 might recognize an epitope common to the proteins of the S100 family (see abstract last sentence). Guignard et al teach that all the S100 proteins have amino acid sequence and secondary-structure similarities in very specific and conserved regions which are the N- and C-terminal hydrophobic amino acid domains. They are also characterized by the presence of two calcium-binding sites called EF-hand, that contain 14 and 12 amino acids. Interestingly, the 14 amino acid EF-hand is conserved in all S100 proteins and is located in a conserved basic domain near the N-terminal part of The protein while the 12 amino acid EF-hand is located in a conserved acidic domain in the C-terminal region. These similarities make the generation of specific antisera difficult due to structural conservation and might explain the cross-reactivity of Mac 387 with MRP-14, MRP-8 and P6. If this mAb recognizes an epitope common to the proteins of S100 family, its use might allow the diction of novel members of this family (see page 106, under Discussion). Given that the human an bovine CAAF1 share 66% sequence homology, the reference MAC 387 would bind the claimed bovine sequence of SEQ ID NO:100, in the absence of evidence to the contrary.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to the SEQ ID NO:19 recited in the claim. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

Applicant's arguments, filed 12/4/08, have been fully considered, but have not been found convincing.

Applicant submits that there is no teaching in either reference of an antibody which is "specific to a calcium-binding protein comprising an amino acid sequence shown in SEQ ID NO:19 or encoded by a nucleic acid sequence shown in SEQ ID NO: 1. Nowhere is there any teaching of a nucleic acid or amino acid sequence in either Guignard or Kelly nor has the Examiner made any allegation of teaching of the sequences. Applicant submits that both references just describe the antibodies and proteins, but nowhere is thee any mention of the antibodies specific to the respective sequences.

However, Applicant's argument attempts to limit the term "specific to a calcium-binding protein" of SEQ ID NO: 19, or encoded by SEQ ID NO: 1 in a manner inconsistent with the well-known and art-recognized specificity of antibody interaction with epitopes defined by particular amino acid sequences. That an antibody "cross-reacts", i.e., binds to more than one protein sequence base on shared epitope, does not mean that the antibody does not "specifically react" with both proteins. As is evidence by Guignard (1996), that the similarities among the S100 family proteins make the generation of specific anti-sera difficult due to structural conservation and might explain the cross-reactivity of Mac 387 with MRP-14, MRP-8 and P6.

Regarding Applicant's comment with respect to Yamamura reference, the examiner notes that the critical date of extrinsic evidence showing a universal fact need not antedate the filing date. See MPEP § 2124.

Applicant's comment with respect to the interference No. 105,501 is acknowledged. However, it is noted that said interference concerned with the protein of SEQ ID NO: 19. The claims are directed to antibodies not proteins. Antibodies are distinct form proteins. Further, in the antibody art, cross-reactivity of prior disclosed antibodies with SEQ ID NO: 19 and the protein encoded by SEQ ID NO: 1 read on the claimed invention.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dell'Angelica (JBC, 269(46): 28929-28936, 1994) as evidenced by the specification disclosure on page 40, lines 6-9, Bost et al. (Immunol. Invest. 1988; 17:577-586), in view of Alisa Campbell (General

properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1).

Dell'Angelica et al teach the primary structure (see Fig. 4) and binding properties of pig calgranulin C, S100-like calcium-binding protein from pig granulacytes. Dell'Angelica et al teach that the pig calgranulin C consists of 91 residues. Sequence analysis predicts two EF-band calcium-binding motifs (see Fig. 8), the first having an extended loop that is distinctive of the S100 protein family. Dell'Angelica et al teach that their results and the calcium-dependent binding of the protein to a phenyl-Superose column strongly suggest that calgranulin C undergoes a gross conformational change upon calcium binding thus supporting the idea that this protein may be involved in Ca2-dependent signal transduction events (see abstract). The reference pig calgranulin C sequence has 79% sequence identity to claimed SEQ ID NO: 19. See below:

```
Qy          1 MTKLEDHLEGIINIFHEYSVRVGHFDTLNKRELKQLITKELPKTLQNTKDQPTIDKIFQD 60
              |||||||||||||||:||||:||:||| |||||||||||| ||:|||| |||||||:
Db          1 MTKLEDHLEGIINIFHQYSVRLGHYDTLIKRELKQLITKELPNTLKNTKDQGTIDKIFQN 60

Qy         61 LDADKDGAVSFEEFVVLVSRVLKTAHIDIHKE 92
              |||::|  |||:|||||: || ||| :|||| 
Db         61 LDANQDEQVSFKEFVVLVTDVLITAHDNIHKE 92
```

The reference pig calgranulin C sequence has 81% sequence identity to claimed calcium-binding protein encoded by a nucleic acid sequence shown in SEQ ID NO: 1. See below:

```
              51ACTAAGCTGGAAGATCACCTGGAGGGAATCATCAACATCTTCCACCAGTACTCCGTTCGG110
                |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db             1 ThrLysLeuGluAspHisLeuGluGlyIleIleAsnIlePheHisGlnTyrSerValArg 20

Qy           111 GTGGGGCATTTCGACACCCTCAACAAGCGTGAGCTGAAGCAGCTGATCACAAAGGAACTT
170
                 :::|||||||:::|||||||||   ||||||||||||||||||||||||||||||||||
Db            21 LeuGlyHisTyrAspThrLeuIleLysArgGluLeuLysGlnLeuIleThrLysGluLeu 40

Qy           171 CCCAAAACCCTCCAGAACACCAAAGATCAACCTACCATTGACAAAATATTCCAAGACCTG
230
                 |||   ||||||:::|||||||||||||||   |||||||||||||||||||:::|||
Db            41 ProAsnThrLeuLysAsnThrLysAspGlnGlyThrIleAspLysIlePheGlnAsnLeu 60

Qy           231 GATGCCGATAAAGACGGAGCCGTCAGCTTTGAGGAATTCGTAGTCCTGGTGTCCAGGGTG
290
                 ||||||:::::::|||      |||||||||:::|||||||||||||||||:::   |||
Db            61 AspAlaAsnGlnAspGluGlnValSerPheLysGluPheValValLeuValThrAspVal 80

Qy           291 CTGAAAACAGCCCACATAGATATCCACAAAGAG 323
                 |||   |||||||||   :::|||||||||||||
Db            81 LeuIleThrAlaHisAspAsnIleHisLysGlu 91
```

Dell'Angelica et al teach that both tryptic (T1-T11) and V8 protease (V1-V11) peptides were separated by RP-HPLC and subsequently submitted to amino acid analysis and/or Edman degradation (see fig. 3 and 4). Dell'Angelica et al teach that the sequence of T9 was identical to that of residues 1-17 (MTKLEDHLEGIINIFHEY, i.e., 100% identical to the N-terminus of the encoded peptide of SEQ ID NO:1) and was assumed to originate from a residual chymotryptic activity. Peptide T3 (QLITK) is 100% identical to the a peptide of SEQ ID NO: 19.

The claimed invention differs from the reference teachings only by the recitation of an antibody specific to a calcium-binding protein comprising an amino acid sequence shown in SEQ ID NO. or encoded by a nucleic acid sequence shown in SEQ ID NO: 1 in claims 22-23.

However, it has been held that once the antigen of interest is selected, the use of that antigen in the known method of Kohler and Milstein will result in the expected hybrid cell lines and the specific monoclonal antibodies. Ex parte Erlich, 3 USPQ2d 1011, 1015 (BPAI 1986).

Moreover, Campbell teaches that it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (see page 3 figure 11.1 in particular). One field of research in which monoclonal antibodies may prove of particular value is in the study of chromosomal proteins. The search for those chromosomal proteins which are responsible for determining cell phenotype has been particularly long and comparatively fruitless and monoclonal antibodies are ideal tools for the dissection of the complex mixture of proteins. As hybridoma production becomes a more routine laboratory technique (see page 29 and 30 under Basic research in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a monoclonal antibody as taught by Campbell against the pig calgranulin C or fragments thereof taught by Dell'Angelica et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because it was customary at the time the invention was made to make monoclonals against any new macromolecule as taught by Campbell.

The resultant antibody would bind to the bovine CAAF1 of SEQ ID NO: 19 as is evidenced by Applicant's specification on page 40, lines 6-9 that the existence of antigen reacting with CAAF1-22-5 monoclonal antibody in human tissue strongly suggests the existence in human tissue of a protein (human CAAF1) homologous with bovine CAAF1. It is noted that human and bovine share only 66% sequence homology. Given the high sequence identity/homology between the referenced/claimed polypeptides (81% or 79%); the resultant antibodies would have the inherent property of binding bovine CAAF1 polypeptide of SEQ ID NO: 19 in the absence of objective evidence to the contrary.

Further evidence came from Bost *et al* that an antibody "cross-reacts", i.e. binds to more than one protein sequence, mean that "specifically bind" with both proteins. Bost et al (Immuno. Invest. 1988 ;17:577-586) describe antibodies which "cross-react" with IL-2 and HIV envelope

protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4-6 residues were identical (see entire document, especially the Abstract and Discussion).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 12/4/08, have been fully considered, but have not been found convincing.

Applicant argues that Applicant submits that claim 22 and 23, which include the limitations of previous claim 21, a claim that was not cited as being obvious in view of the cited references, should now be allowed.

However, the claims 22 and 23 are drawn to product not a method as canceled claim 21.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 31, 2009

/Maher M. Haddad/
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Primary Examiner
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